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From NMP to RAFT and Thiol-Ene Chemistry by In Situ Functionalisation of Nitroxide Chain Ends[a]

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Summary: A straightforward, novel strategy based on the in situ functionalisation of polymers prepared by nitroxide mediated polymerization (NMP), for the use as an extension towards block copolymers and post-polymerisation modifications, has been investigated. Styrene and isobornyl acrylate have been polymerised by NMP and, before the reaction was terminated, the nitroxide end-group was exchanged for a thiocarbonylthio end-group by means of a rapid transfer reaction with bis(thiobenzoyl) disulfide to generate in-situ reversible addition-fragmentation chain transfer (RAFT) macroinitiators. Moreover, not only have these macroinitiators been used in chain extension and block copolymerisation experiments by the RAFT process, but a thiol-terminated polymer was also synthesised by aminolysis of the RAFT end-group and subsequently reacted with dodecyl vinyl ether by thiol-ene chemistry.

Nitroxide Mediated Polymerisation (NMP) was discovered more than 20 years ago[1, 2] and has been recognised since then as a straightforward method for the controlled radical polymerisation of various monomers including styrenics[2], acrylates[3], methacrylates (under

[a] **Supporting Information** is available at Wiley Online Library or from the author.

specific conditions)[4-7], acrylamides[8], acrylonitrile[9], and even 1,3-dienes[10-12]. Furthermore NMP allows for the design of complex macromolecular architectures such as block, graft and star copolymers[9, 13, 14]. The technique is based on reversible termination of the propagating chains in the presence of a nitroxide[15]. For a polymerisation to be controlled, the equilibrium must be shifted towards dormant species in order to minimise termination. Also, the exchange between active and dormant species must be several orders of magnitude faster than the propagation itself to ensure that all chains statistically grow at the same time[16]. Thus, one of the main features of NMP is that the nitroxide end-group is retained onto the polymer chain-end after the polymerisation. This can be an advantage for the synthesis of block copolymers as the polymerisation can be reinitiated in presence of a second monomer[9]. However, there is an interest in removing the nitroxide end-group, for example to improve thermal stability[17] or introduce functional groups[1, 18, 19]. Furthermore, there is a growing trend for combining different polymerisation methods for the synthesis of new copolymers, which cannot be obtained by one technique only[20-22].

Another controlled radical polymerisation method of interest is reversible addition-fragmentation chain transfer (RAFT) polymerisation[23]. Its concept relies on the use of a thiocarbonylthio compound as a chain transfer agent (CTA) to create a living free-radical polymerisation system as first described in 1998[24]. The CTA satisfied the criteria for living polymerisation since the products obtained exhibited narrow polydispersity indexes, linear evolution of the number average molar mass (M_n) with conversion and an agreement with theoretical M_n. In addition, the end-groups of the polymer chains retain the CTA, thus allowing further chain growth or block extension to occur upon subsequent monomer addition[25]. The thiocarbonylthio end-group fidelity is not only an illustration of the living character of the RAFT polymerisation but also an important feature for further post-

polymerisation experiments. For example, thiol end-groups can easily be generated from the CTA[26] and used to introduce different functionalities through thiol-ene chemistry[27, 28].

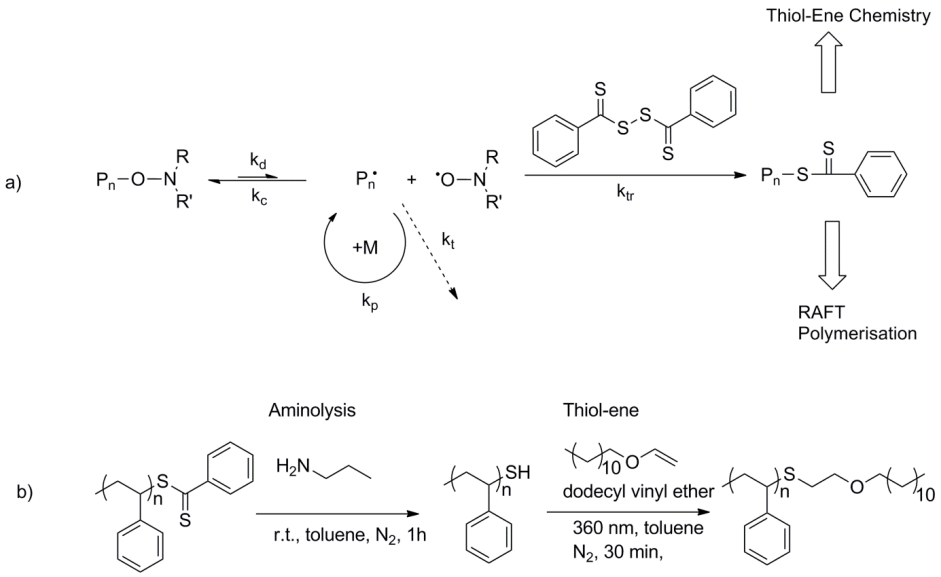
RAFT polymerisation provides the ability to control polymerisation of the most employed monomers such as acrylics, methacrylics, styrenics, dienes, and other vinyl monomers[23]. It is tolerant to unprotected functionalities (e.g. OH, NR_2, CO_2H, SO_3H, $CONR_2$) in monomer, solvent and initiating system[29]; it is also compatible with a wide range of reaction conditions[23, 30] (e.g. bulk, organic or aqueous solution, emulsion, mini-emulsion, suspension). In addition, it is simple to implement for both research and industrial purposes[31]. The well-defined complex macromolecules made by RAFT have been proven to be efficient to build nanostructures such as micelles, vesicles, and nanoparticles of either synthetic or synthetic polymers combined with biomolecules or inorganic nanoparticles[23].

We recently reported a technique for the one-pot removal of nitroxide during NMP with the use of highly active transfer agents such as thiols, radical initiators and CBr_4 in order to obtain thermally stable polymers[32]. Furthermore, the use of the latter allowed for the in situ bromination of the polymer chain-ends. Consequently, this bromine terminated precursor was successfully used in chain extension experiments by atom transfer radical polymerisation (ATRP). This motivated us to investigate the possibility to switch from NMP to RAFT polymerisation in a one-pot approach through in situ functionalisation and to provide at the same time an extension towards thiol-ene chemistry.

As reported in the literature, disulfides are well known as chain transfer agents in free radical polymerisation[33]. For example, cyclic and linear disulfides were used by Tobolsky and Baysal[34] to be incorporated into polystyrene (PS), yielding polymers with variable sulphur content. Shanmugananda Murthy et al.[35] showed that poly(styrene disulfide) was an efficient chain transfer agent in the conventional radical polymerisation of styrene (S), with transfer constants in the order of 6 to 9.10^{-2}. Otsu et al.[36] determined the chain transfer

constants of substituted diphenyl disulfides in radical bulk polymerisation of methyl methacrylate (MMA) and observed that the substituent on the phenyl rings had noticeable effects on the reactivity of the disulfide towards the PMMA radical. Beyou et al. functionalised polymers bearing nitroxide end-groups in presence of thiuram disulfides in a two steps process[37]. More recently, the group of Rizzardo[38] studied the effect of diphenyl and dibenzoyl disulfides as CTA in the polymerisation of the cyclic monomer 7-methylene-2-methyl-1,5-dithiacyclooctane (MDTO), and they observed that diphenyl disulfide presented a higher chain transfer constant, presumably as a result of an increase of the resonance stabilisation of the resulting radical.

As all these studies clearly show the suitability of disulfides as chain transfer agents, the controlled addition of bis(thiobenzoyl) disulfide during NMP was investigated in this research (Scheme 1a). Bis(thiobenzoyl) disulfide is readily available but can also easily be synthesised in the laboratory[39]. The end-group modification of the NMP synthesised polymers with this compound is not only expected to remove the dormant nitroxide moiety but also to provide, in one-pot, a thiobenzoylthio polymer chain-end. The resulting polymer can subsequently be used as a RAFT precursor, which can be employed for chain extension experiments. Furthermore, the RAFT end-group can be reduced to a thiol by aminolysis in a post-polymerisation reaction, followed by functionalisation through thiol-ene chemistry (Scheme 1b).



Scheme 1a) One-pot nitroxide removal and route towards RAFT polymerisation and thiol-ene chemistry. **b)** Functionalisation of PS (entry 1, Table 1): aminolysis and UV assisted radical thiol-ene reaction.

Table 1 Experiments for one-pot removal of nitroxides from NMP polymers with bis(thiobenzoyl) disulfide[a].

Entry	M[b]	Initiation[c]	DP[d]	Disulfide Eq.[e]	$t_i - t_f$[f] (min)	$M_{n,i} - M_{n,f}$[g] ($g.mol^{-1}$)	$PDI_i - PDI_f$[h]	End-Group Fidelity[i] (%)
1	S	AIBN / SG1 (1 / 3)	139	0.7	240 – 250	4,200 – 4,300	1.12 – 1.10	99.9[j]
2	S	BlocBuilder MA	71	1.9	120 – 130	4,500 – 4,500	1.11 – 1.12	99.9[k]
3	iBA	AIBN / SG1 (1 / 2)	100	1	360 – 370	5,800 – 5,900	1.14 – 1.14	50.6

[a] Temperature: 120 °C; further details on the polymerisation conditions can be found in the Supporting Information. [b] M = monomer. [c] initiator / nitroxide molar ratio is given between brackets for bimolecular systems. [d] Theoretical degree of polymerisation at 100% conversion. [e] Bis(thiobenzoyl) disulfide equivalents compared to the nitroxide. [f] t_i = bis(thiobenzoyl) disulfide injection time; t_f = final reaction time. [g] $M_{n,i}$ = molar mass just before bis(thiobenzoyl) disulfide injection; $M_{n,f}$ = molar mass at the end of the reaction. [h] PDI_i = PDI just before bis(thiobenzoyl) disulfide injection; PDI_f = PDI at the end of the reaction. [i] CTA end-group fidelity determined by elemental analysis. [j,k] The measured values of resp. 113 and 108 %, as a result of experimental error, have been rounded to 99.9 %.

The effectiveness of bis(thiobenzoyl) disulfide as chain transfer agent in NMP was tested in three model experiments (Table 1). NMP of styrene – with bimolecular (entry 1) or unimolecular (entry 2) initiator systems – and isobornyl acrylate (entry 3) was performed in bulk in the presence of N-*tert*-butyl-1-diethylphosphono-2,2-dimethylpropyl nitroxide (SG1). Bis(thiobenzoyl) disulfide, dissolved in a minimal amount of solvent, was added to the crude reaction mixture after a predetermined reaction time (see the Supporting Information for more information on experimental conditions). The influence of the concentration of the bis(thiobenzoyl) disulfide compound, ranging from 0.7 to almost 2 equivalents compared to

SG1, has been studied. From the values in Table 1, it can be clearly noticed that, after addition of the chain transfer agent, the polymerisation was stopped as no molar mass increase was observed and polydispersity index values (PDI) values remained the same, both for styrene (S) and isobornyl acrylate (iBA). Figure 1a shows photographs of the purified PS sample (entry 1) before and after addition of bis(thiobenzoyl) disulfide. While the polymer samples were purified by repeated precipitations in a ten-fold excess of a non-solvent, the resulting thiobenzoylthio terminated polystyrene (PS) and poly(isobornyl acrylate) (PiBA) show the characteristic pink colour after in situ functionalisation, which constitutes an additional proof for the effectiveness of the method employed.

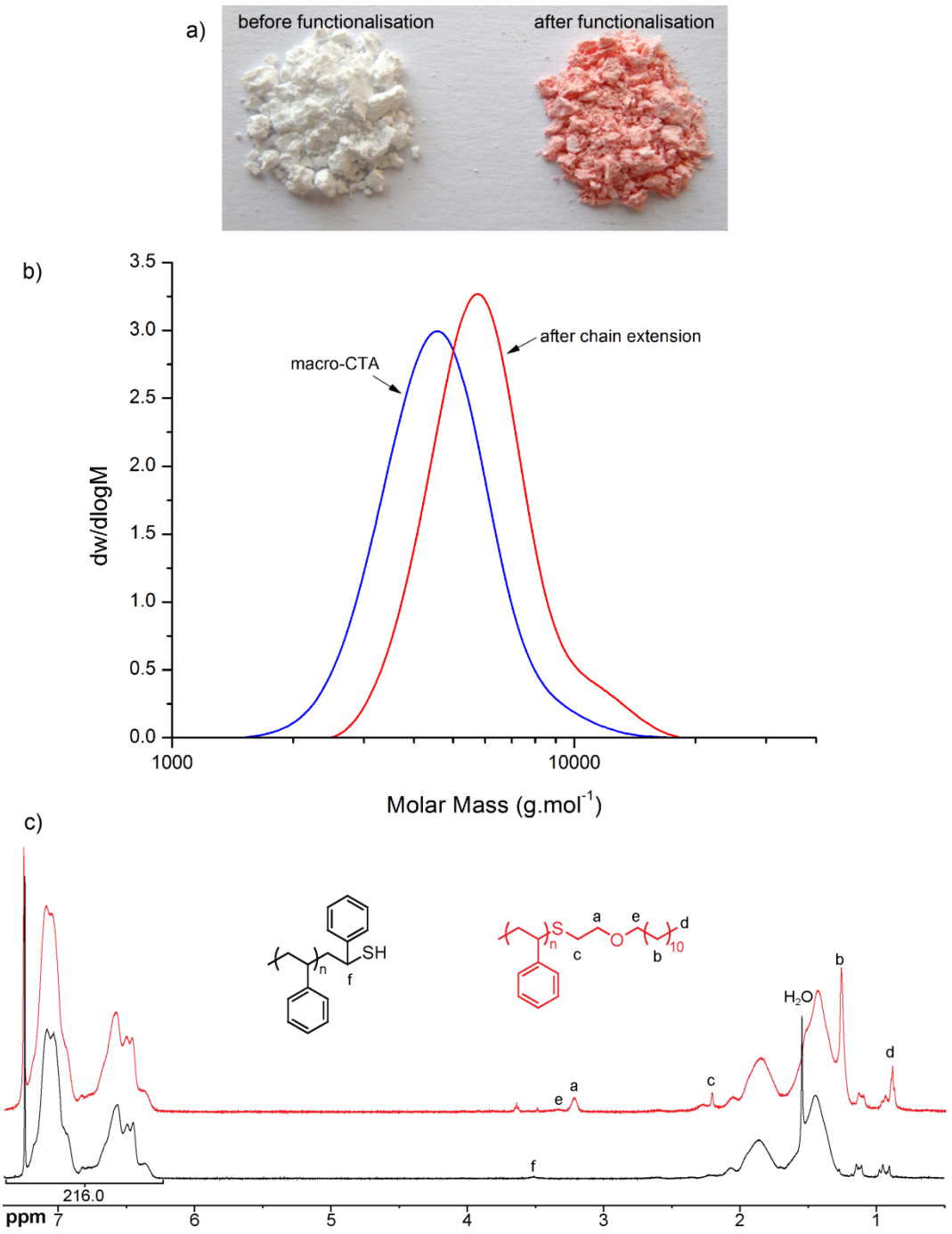


Figure 1a) Photographs of PS synthesised by NMP (entry 1, Table 1) before (left) and after (right) bis(thiobenzoyl) disulfide addition. **b)** Molar mass distribution before (left) and after (right) chain extension of a PS macro-CTA (entry 2, Table 1) by RAFT polymerisation (entry 4, Table 2). **c)** ^{1}H-NMR 500 MHz ($CDCl_3$) spectrum of thiol-containing PS before (bottom) and after thiol-ene functionalisation (top) with dodecyl vinyl ether (Scheme 1b).

The end-group fidelity was determined by elemental analysis (Table 1) after the functionalisation reaction on samples purified by repeated precipitations. Remarkably, the thiobenzoylthio functionalisation was quantitative for PS (entries 1,2, Table 1), only 10 min after addition of bis(thiobenzoyl) disulfide. On the other hand, the end group

functionalisation in the case of PiBA (entry 3, Table 1) was much lower, which might be explained by the bulkiness of the isobornyl group that is known to reduce the segmental mobility of the growing chains in free radical polymerisation relative to other acrylic monomers[40]. The outcome might be a slower transfer to the disulfide during NMP, which results in this incomplete functionalisation.

Table 2 Chain extension and block copolymerisation by RAFT polymerisation from macro-CTA[a].

Entry	Ma-CTA[b]	t (min)	$M_{n,i}$[c] (g.mol^{-1})	PDI[c]	$M_{n,f}$[d] (g.mol^{-1})	PDI[d]
4	PS-CTA (entry 2)	480	4,500	1.11	5,600	1.10
5	PiBA-CTA (entry 3)	120	5,900	1.14	12,600	1.59

[a] Monomer: styrene; $[M]_0$/[Ma-CTA]/[AIBN] = 300/1/0.2; temperature: 90 °C (Further details on the polymerisation conditions can be found in the Supporting Information). [b] Ma-CTA = macroinitiator. [c] Molar mass and PDI of the macroinitiator. [d] Molar mass and PDI after chain extension.

The successful functionalisation of PS with bis(thiobenzoyl) disulfide during NMP was used to perform a chain extension of the PS macro-CTA with styrene (entry 4, Table 2). From literature, it is expected that this type of macro-CTA based on dithiobenzoate CTA's will be efficient for the RAFT polymerisation of, at least, styrenic and acrylic based monomers[25]. In a typical procedure, an overall ratio of 300/1/0.2 between styrene, macro-CTA and AIBN was employed (see the Supporting Information for further details). An initial monomer solution (25 vol%) in toluene was employed and the monomer was added step-wise every two hours in order to have a better control over the polymerisation.

Figure 1b shows the SEC chromatograph obtained for the chain extension experiment. A noticeable shift can be observed after 8 hours of reaction at 90 °C, which is a clear evidence for the ability of the macro-CTA to polymerise styrene by the RAFT process and thus for the suitability of the functionalisation procedure. In addition, no shoulder at low molar masses is observed, indicating that the chain extension proceeded in a controlled fashion. The polymerisation was found to be relatively slow due to the occurrence of

retardation, which is a well known phenomenon for RAFT polymerisation with dithiobenzoate CTA's[41]. As expected, when performing a RAFT polymerisation experiment under the same conditions with the PiBA-sample (entry 3), a much higher polydispersity index was observed because of the uncomplete end group functionalization (entry 5, Table 2). The thiocarbonylthio functional group on the polymer chain-end can easily be transformed into a thiol functionality in one step under mild conditions[42]. Subsequently, this thiol can be used for various post-modification reactions[26]. Here, we investigated the possibility to perform thiol-ene click chemistry after transforming a PS macro-CTA (entry 1, Table 1) into a thiol-terminated polymer through aminolysis (Scheme 1b). More specifically, the mercapto-functionalised PS was obtained by propylamine induced aminolysis, following a slightly modified version of the procedure reported earlier by our group[28] (see the Supporting Information for more details). The reaction proceeds with a 20 molar equivalents of amine per mol of thiocarbonylthio group, generating the desired thiol-terminated polymer in the presence of tributyl phosphine as a reducing agent to avoid disulfide coupling. Both the UV spectra of the parent and modified PS (Figure S5 in the Supporting Information) as well as the SEC traces of the polymer before and after aminolysis were recorded (Figure S6 in the Supporting Information). These experiments confirmed the completeness of the reaction, without observation of disulfide formation. Consequently, the thiol-containing PS was subjected to thiol-ene reaction with dodecyl vinyl ether, in the presence of 2,2-dimethoxy-2-phenylacetophenone (DMPA) as UV cleavable photoinitiator, to afford PS with modified chain-end structure within 30 minutes (Scheme 1b). The thiol-ene chemistry allowed successful polymer modification under 360 nm irradiation, as evidenced by the appearance of new signals in the ^{1}H NMR spectrum (Figure 1c), corresponding to both the methylene protons from the newly formed ether bond (peak a, 3.22 ppm) and to the protons of the alkyl

chain of dodecyl vinyl ether (peak b, 1.27 ppm). Furthermore, a good agreement was found with NMR data previously reported for a similar thiol-ene reaction[28].

In conclusion, by applying a one-pot procedure and in situ functionalisation, it was possible to extend NMP towards RAFT and thiol-ene chemistry. Through the use of bis(thiobenzoyl) disulfide, polymer chains prepared by NMP were transformed into thiocarbonylthio-terminated polymers. These polymers were subsequently used as macro-CTA in RAFT polymerisation. Copolymerisation and chain extension experiments were performed. In addition, a PS macro-CTA was chemically modified by aminolysis as a post-polymerisation process, yielding a thiol-terminated polymer that was subsequently employed for thiol-ene chemistry.

The straightforward strategy presented in this work offers to our knowledge for the first time an efficient transformation between two of the most employed controlled radical polymerisation techniques, namely NMP and RAFT, and also provides a pathway from NMP to thiol-ene 'click' chemistry.

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Keywords: block copolymers; functionalisation of polymers; nitroxide mediated polymerisation; reversible addition-fragmentation chain transfer; thiol-ene chemistry

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Table of Contents

A strategy based on the controlled addition of a disulfide during NMP is investigated for the synthesis of macro-CTA's. These compounds are subsequently used to obtain block copolymers by RAFT polymerisation and also reduced to thiols for further functionalisation of the polymer chain-ends by thiol-ene chemistry.